

Hydrazoic Acid and Azides

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1. Introduction

Organic and inorganic azides have gained greater significance in the last few years. Sodium azide, for example, is produced all over the world at volumes of 1 000 t/a [1]. Nowadays azides are not only applicable as detonators and propellants by releasing huge amounts of nitrogen gas [2] and for fine chemical syntheses, but also as bioorthogonal chemical reporters [3] and for drug design (e.g., zidovudine) [4]. Hydrazoic acid (HN_3) [5] itself has little industrial significance as it is highly toxic and explosive [6] (see Section 4.2) [7]; the most important salts are sodium azide and lead azide [1] as well as silver and barium salts. Especially the heavy metal azides tend to be highly explosive. Organic azides [7, 8] are derivatives of hydrazoic acid (see Section 8.2), and they are very useful in organic syntheses.

The oldest process for preparing both the acid and its salts is based on diazotization of hydrazine and its salts [9, 10]. The method still most widely used today for the production of

sodium azide is the reaction of sodium amide with dinitrogen monoxide (see Section 4.1). This process was introduced industrially in 1924, but has not been patented until 1935 [11].

The original use of sodium azide was the safe production of lead azide, a fulminating (detonating) agent via salt metathesis reaction. Lead azide now constitutes only a small part of the total consumption of the sodium azide. By far the major proportion is used in the organic chemical industry. Increasing importance is ascribed to the use as a gas generator fuel that produces nitrogen.

The toxicity and the unsettled question of potential carcinogenicity [12, 13] make special workplace safety measures imperative. Sodium azide is the most commonly produced azide; the next section summarizes the properties, syntheses and uses of this salt.

The azide moiety is a so-called pseudohalide and therefore many physical (e.g., solubility) and chemical properties (e.g., polarity) of organic and inorganic azides can be compared to the corresponding halides.

2. Physical Properties of Sodium Azide

Sodium azide [26628-22-8] (also called smite, sodium trinitride, or azium) (NaN_3) is a white, odorless (with traces of water fishy smelling because of HN_3 formation), crystalline substance, which is well soluble in water and ammonia and insoluble in most organic solvents, except very polar ones like dimethylformamide or dimethylsulfoxide. Some physical properties of sodium azide are listed below:

M_r	65.01
pK_b	9.3
mp	275°C (decomposition)
Density (20°C)	1.846 g/cm ³
Vapor pressure (20°C)	1 Pa
Solubility in 100 mL water (17°C)	42.0 g

3. Chemical Properties of Sodium Azide and Hydrazoic Acid

Sodium azide decomposes fast or explosively at 300°C, forming sodium metal and nitrogen gas. In contact with fire, azides form toxic nitrogen oxides. Compared to heavy metal azides, the sodium salt is easier to handle because it is less explosive. As common to all azides, the sodium salt is also sensitive to shock, friction, and moisture. Alkyl and acyl halides react with sodium azide to the corresponding alkyl and acyl azides via a nucleophilic substitution reaction (see Section 8.3). Sodium azide is also used in the Curtius reaction for the production of amines [14]. For further details of organic syntheses with HN_3 and NaN_3 , see Section 8.3.

Acidification of sodium azide produces volatile, explosive and toxic hydrazoic acid ($bp = 36^\circ\text{C}$) which is a weak Brønsted acid ($pK_a = 4.7$) [6]. Particularly in the concentrated or pure state the liquid is very explosive. Thus, many procedures have been developed to decrease the amount of hydrazoic acid, e.g., by using buffered solutions [15].

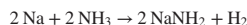
Free hydrazoic acid reacts with solutions or slurries of alkali-metal or alkaline-earth

hydroxides, carbonates, and hydrogen carbonates to give solutions of the corresponding azides, which can be obtained in pure form by evaporation. Hydrazoic acid is also capable of reacting with pure metals, e.g., copper, to form the metal azide salt.

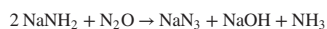
4. Production

4.1. Sodium Azide

The most important production process has been developed from the work of WISLICENUS, first published in 1892 [16]. It consists of two steps. In the first step, ammonia is fed into molten sodium metal, which is contained in a closed steel vessel at 350°C:



In the second step the resulting liquid sodium amide is converted to sodium azide, sodium hydroxide, and ammonia by reaction with dinitrogen monoxide at approximately 230°C in a horizontal nickel reactor:

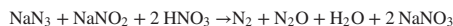


The solid mixture is known as crude azide. Part of the crude azide is left in the reactor for the next charge; this gives better distribution of the added sodium amide and also improves the conversion.

Dinitrogen monoxide is generated by decomposition of a 50% ammonium nitrate solution at 230°C. The latter is prepared by absorption of the ammonia liberated in the second stage and that remaining from the first stage in 50% nitric acid. An additional absorption medium is spent acid from the nitration processes that has been recycled and worked-up. Nitric acid oxidation of the waste from adipic acid production also gives dinitrogen monoxide [17].

To isolate sodium azide, the crude azide is dissolved in water and the resulting solution is clarified and then evaporated. The separated residual crystalline material is dried at 110°C and may be used or shipped after the agglomerates have been broken up.

The mother liquor must be evaporated at least twice. While this is being done, any residual sodium azide is decomposed by the addition of sodium nitrite and dilute nitric acid:



The yield based on sodium is about 90%, when the formation of an equimolar amount of sodium hydroxide is taken into account.

In addition to the toxicity of the final product, the risk of explosion of the gas mixture is a potential hazard. Sodium amide reacts vigorously with water.

A variation of the Wislicenus process uses sodium monoxide and consists of a single step [18]:



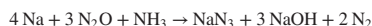
Ammonia can be replaced, wholly or in part, by sodium amide:



No gas is liberated in this process, which may thus be run at elevated pressure.

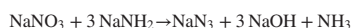
Formation of sodium amide in liquid ammonia [19–21] and azide reaction in liquid ammonia or high-boiling hydrocarbons [11, 22] have also been reported.

When dinitrogen monoxide is added before amide formation is complete, nitrogen is given off in the one-step reaction rather than ammonia. The yield of sodium azide with respect to sodium hydroxide is less favorable [23–26]:



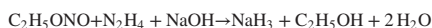
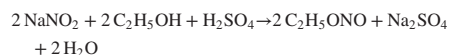
Liquid ammonia [21, 27–29] or ethanol [22] can be used to separate sodium hydroxide from sodium azide.

Melting sodium amide together with sodium nitrite at 175°C is another alternative route leading to sodium azide with ammonia and sodium hydroxide as byproducts:



By following the pioneering experiments of CURTIUS and THIELE, the production of sodium azide for laboratory purposes by diazotization of

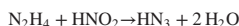
hydrazine has been further developed. The ethyl nitrite required for this reaction is produced from ethanol and sodium nitrite. A serious drawback to the use of this process is the carcinogenicity of hydrazine and its salts (see → Hydrazine) [1, 30–32].



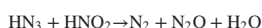
There are also a few other reactions that furnish sodium azide but only in low yields or as byproducts [33].

4.2. Hydrazoic Acid

Originally hydrazoic acid was synthesized by reacting excess hydrazine monohydrate with nitrous acid using an additional acid source (e.g., nitric acid or perchloric acid) reaching at least a concentration of 1 mol/L [34]:



The produced hydrazoic acid also reacts with the nitrous acid forming gaseous byproducts:



Because of this side reaction the produced hydrazoic acid is always limited to small amounts. Therefore, hydrazoic acid [35] is better liberated as a gas by decomposition of sodium azide (also viable with barium azide) [36] solution with dilute sulfuric acid (or stearic acid) [33]. A nonexplosive gas mixture is formed by simultaneous dilution with air or nitrogen to a concentration of less than 15%. Aqueous solutions of ca. 10%, which are safe to handle, can be obtained by concentration of dilute solutions. Solutions with a hydrazoic acid content in excess of 20% are liable to decompose explosively.

There are also a few other reactions which are leading to hydrazoic acid but only in low yields or as byproducts [33].

5. Quality Specifications and Analysis

In accordance with manufacturers' specifications, sodium azide must fulfill the following requirements:

Color, form	White, crystalline
Azide content	99.0% (min.)
Alkalinity	0.1% (max.)
Water	0.1% (max.)
Insolubles	0.1% (max.)
Chloride (as NaCl)	0.05% (max.)
Sulfate (as BaSO ₄)	0.05% (max.)
Carbonate	0.05% (max.)
Nitrate	0.05% (max.)
Iron	0.05% (max.)

The azide content is determined titrimetrically by addition of excess cerium (IV) salt and back titration with oxalic acid.

On testing for nitrate, acidic diphenylamine solution must not turn blue when sodium azide is added.

Azides may be detected with strips of filter paper soaked in 10% iron(III) chloride solution. This test is highly sensitive because of the formation of the intensely colored complex ion $[\text{Fe}(\text{N}_3)_6]^{3-}$.

6. Storage and Transportation

Dry sodium azide is stable for years if stored in sealed containers at room temperature. Sodium azide is packed in sheet-iron drums lined with polyethylene sacking.

In accordance with regulations concerning dangerous substances, sodium azide must be marked as a poison. The MAK value is 0.2 mg/m³ [37].

Transportation codes:

IMDG (GGVSee):	Class 6.1 D E-F 6165 UN no. 1687
RID (GGVE):	Class 6.1 Rn 601, Section 42 b
ADR (GGVS):	Class 6.1 Rn 2601, Section 42 b
ADNR:	Class 6.1 Rn 6601, Section 42 b
EEC Directives/ GefStoffV:	011-004-00-7
United Kingdom Blue Book:	Poison and IMDG Code E 6165
United States CFR 49:	Paragraph 172.101 Poison B
ICAO/IATA-DGR:	Class 6.1 UN no. 1687
RTECS-no.:	VY8050000

UN-no.:	1687
EU-no.:	011-004-00-7
EINECS-no.:	247-852-1

Hazard pictograms:



GHS coding:	GHS06, GHS07
Hazard statements:	H300, H410, EUH032
Precautionary statements:	P273, P308 + P310

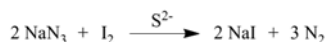
Because of its highly explosiveness, hydrazoic acid is seldom commercially available and therefore only the data of sodium azide, being a precursor to hydrazoic acid, is mentioned here.

7. Application of Sodium Azide

Sodium azide is the starting material for the synthesis of other metal azides like $\text{Pb}(\text{N}_3)_2$, important for the explosive industries, as well as for many organic azides, such as tosyl azide or tertiary alkyl azides, which are essential in fine chemical syntheses [38]. Because nitrogen is released during thermal decomposition of sodium azide (at 300°C), it is also used as a source for pure nitrogen gas. Moreover, sodium azide is used in automobile safety devices, e.g., steering-wheel airbags and in escape chutes where instantaneous delivery of cold, dust-free, and nontoxic gas is of the utmost importance. The sodium metal, formed by thermal decomposition, is oxidized and reacts with silicon oxide or boron oxide to form sodium silicate or borate, respectively [39]. However, due to its toxicity it has been replaced by other nitrogen rich propellants since 1995.

In analytics, a combination of sodium azide and iodine can be used for the titration of sulfur compounds containing thiols or thioethers like penicillin. Therefore, an aqueous solution of sodium azide and a defined amount of iodine (and catalytic amounts of sodium thiosulfate) is used, while the vanishing color of iodine marks the end of the titration. Iodine is only able to react with those thio compounds, when azides are present. The so-called iodine-azide reaction

is very sensitive [40]:



Sodium azide is also utilized in all areas where sterile laboratory equipment is necessary, since it is able to destroy different microorganisms by blocking the oxygen-binding pocket in the active center of cytochrome oxidase [41].

The salt is also employed against hypertension in case of emergency [42] and as a nitrification inhibitor [43].

8. Other Derivatives and Salts

8.1. Metal Salts

Heavy metal azides are easily accessible via salt metathesis reaction in aqueous solution. Only the most important inorganic metal azides are listed [44, 45].

Measurements of the explosiveness suggest the following order of impact sensitivity:

Alkali azides < TiN_3 < AgN_3 < $\text{Ba}(\text{N}_3)_2$ < $\text{Pb}(\text{N}_3)_2$ < copper azides [46].

Other alkali-metal azides (Li, K, Rb, Cs) can be prepared by the same route, but they do not have any advantages over NaN_3 .

Lead azide [85941-57-7] is used as a detonating (fulminating) agent [47–55] (see → Explosives). The actual content of lead azide depends on the purpose for which it is required. The range is from 80% to almost 100%. The product must not contain needle-shaped crystals. Crystal growth to produce spheroids is controlled by addition of dextrin, gelatin, carboxymethyl cellulose, and polyhydroxy polycarboxylic acids or their soluble salts.

Silver azide [13863-88-2] is also a very explosive reagent and is able to detonate even by exposure to UV-irradiation. It has, however, some advantages over the less expensive lead azide in certain electrical ignition systems [56]. In 1996 silver azide was proposed as a suitable replacement for lead azide.

Copper Azides. Copper azide, CuN_3 , [14215-30-6] and copper diazide, $\text{Cu}(\text{N}_3)_2$ [14336-80-2] are hazardous products [57, 58] that are likely to form when sodium azide powder and hydrazoic acid are being handled. Copper azides form on objects made of copper or brass and tend to decompose explosively under mechanical load. Sieves and dust or oil filters of pumps must be free of copper whenever a risk of contact with azides is present.

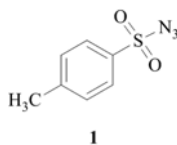
Barium azide [18810-58-7] is used in fluorescent light tubes to improve the light yield [59, 60].

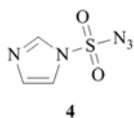
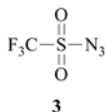
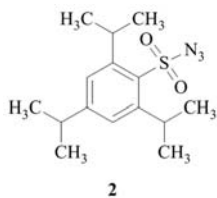
Ammonium azide [12164-94-2] is a possible propellant [61, 62]. In contrast to other azides, it is not shock sensitive and can be purified by sublimation.

8.2. Organic Azides in Fine Chemical Synthesis

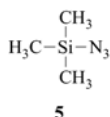
A number of organic azides have been used, not only in research laboratories [7] but also in fine chemical synthesis (1 kg to several hundred kilograms). The most important production method is the conversion of halide (or other good leaving groups) compounds with sodium azide to the corresponding azide derivative. It is also possible to synthesize many organic aryl azides by building up aryl pentazols (diazonium–azide reaction) followed by extrusion of nitrogen or via the Dutt–Wormall reaction [63]. Some of the most relevant organic azides are listed below:

Tosyl azide (TsN_3 , **1**) [941-55-9] is, like other sulfonyl azides, such as trisyl azide [36982-84-0] (**2**) [61, 62], triflyl azide [3855-45-6] (**3**) or imidazole-1-sulfonyl azide [952234-37-6] (**4**) a source for azide cations, e.g., for enolate azidations [64, 65] and also a diazo transfer reagent [66]. This commercial product is obtained from tosyl chloride and sodium azide and is one of the more stable organic azides, but still a potential explosive.



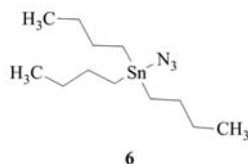


Trimethylsilyl azide (TMSN₃, TMSA or Me₃SiN₃, **5**) [4648-54-8] can be formed from trimethylsilyl chloride and sodium azide. It is sensitive to hydrolysis releasing highly toxic HN₃. As both materials have different IR spectra, in situ monitoring is possible [67]. Often it has been used in Mitsunobu reactions [68] and for the preparation of carboxylic azides. Because of its good solubility in organic solvents it is often applied to convert aryl diazonium salts into the corresponding aryl azides [69].

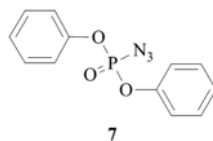


Tributyltin azide (TBSnA or Bu₃SnN₃, **6**) [17846-68-3] [70] is produced from tributyltin chloride on kilogram scale (e.g., HBCChem produces 100 kg) and is used for the synthesis of tetrazole-based pharmaceuticals [71–82], such as sartans (e.g., Valsartan [79]). Disadvantages of tributyltin azide are the high toxicity and the very strong odor which is well absorbed by any material and hard to remove [83, 84].

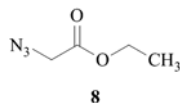
The lower alkyl compounds are often replaced by the higher homologous or organoaluminum azides because they are less toxic [85].



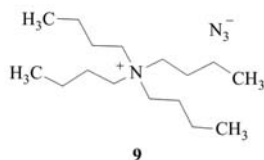
Diphenylphosphoryl azide (DPPA, **7**) [26386-88-9] [7, 86] is a very toxic and explosive reagent which is used in multikilogram scale syntheses of, e.g., huperzine A and other active pharmaceutical ingredients. It is also applied to generate acyl azides required for the Curtius rearrangement [87, 88]. It can be destroyed by adding acetic acid. Additionally, DPPA serves also as an azide source in Mitsunobu reactions [87].



Ethyl azidoacetate (AAE, **8**) [637-81-0] [1] is prepared from ethyl chloroacetate and sodium azide. Because of its explosive properties, it is only transported in diluted solution in various solvents. It is widely used for the synthesis of heterocycles like aziridines [89], pyrroles [90] and indoles [91].



Tetrabutylammonium azide (TBAA, **9**) [993-22-6] [1] is a very good phase transfer reagent and can be synthesized by conversion of tetrabutylammonium halides with sodium azide. It is applicable in the synthesis of tetrazoles starting from nitriles and also as a source of azide anions for nucleophilic substitutions.



8.3. Organic Reactions of Azides

Sodium azide is used in organic synthesis under very strict safety precautions. Reactions with sodium azide or its solutions may be carried out in plastic, glass, or enameled vessels that are free of exposed metal parts. Solid sodium azide is best stored in plastic containers. Before reactions are performed, all apparatus must be checked for bare metal parts because of possible explosive heavy metal azide formation. Overheating of individual parts, (e.g., agitator shafts) should be avoided. Care must be taken to remove the poisonous and highly explosive gases resulting from formation of hydrazoic acid, and effective protection against explosion must be provided.

Reactions with sodium azide or hydrazoic acid with electrophiles [92] enable access to a series of organic azides and derivatives. In the next paragraphs some essential reactions of azide compounds are depicted.

Substitution Reactions. The S_N2 reaction of alkyl halides [93] (chlorides [94] or bromides) or alkyl sulfonates (such as mesylates [95, 96], brosylates [97], triflates [98] or tosylates) with sodium azide is generally applicable in the aliphatic series. Dimethylformamide is particularly suitable as solvent. The chlorinated solvents react with sodium azide to form polyazidoalkanes, which are hazardous. In addition, methyl and ethylammonium salts (frequently used for phase-transfer catalysis) might react with azide ions to form hazardous methyl or ethyl azide, respectively [99].

Alcohols can be converted via Mitsunobu reactions [68].

Acid chlorides react rapidly, producing the carbonyl azide necessary for the Curtius rearrangement [100]:

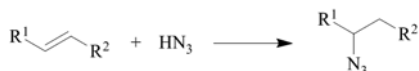


Carbonyl azides are also used in peptide synthesis [101] because the reaction with amino acids proceeds under such mild conditions that the stereochemistry is retained [102]. The required carbonyl azides can be synthesized from acylhydrazines via diazotation [102]. Particularly active esters and tertiary alcohols can also react with metal azides to yield the corresponding azides.

Aromatic diazonium salts react with azide ions via pentazoles to (shock sensitive) aryl azides [92, 103]:



Addition Reactions. Olefins react with hydrazoic acid to form alkyl azides:



Isocyanates are transformed to carbamic acid azides. Ketenes form acid azides. *Trans-α*-azidoalcohols are formed from epoxides.

Salt Formation. Amines and phosphines form salts with hydrazoic acid. For example, triphenylphosphine reacts with two equivalents of hydrazoic acid to produce the triphenylphosphine-iminium salt.

Cycloadditions (“Click” Chemistry). Organic azides react with alkenes and alkynes to form 4,5-dihydro-1H-1,2,3-triazolines and 1H-1,2,3-triazoles, respectively. The latter are formed under mild conditions by copper-catalysis, with electron deficient alkynes, or from metalated alkynes (“Click” reaction) [65]. Rufinamide is produced by reaction of a benzyl azide and a propiolic acid derivative [104].

Activated alkynes also react with sodium azide [105].

Triazoles can also be formed from nitriles by a Dimroth cyclization [106].

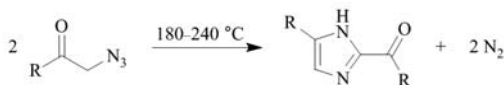
Tetrazoles are accessible from sodium azide and nitriles [15, 107] or from tributyltin azide (see above).

Rearrangements. The Schmidt rearrangement converts ketones into amides and carboxylic

acids into amines, using hydrazoic acid. To circumvent the handling of this dangerous reagent, microreactors have been used [108].

The Curtius rearrangement converts acyl azides into isocyanates [100, 109]. This has been used in flow chemistry [110], for example, for the preparation of PARP-1 inhibitors [111].

Miscellaneous Reactions. Organic azides are used as starting materials for the preparation of heterocyclic compounds, such as imidazoles, oxazoles, 1,2,3-triazoles, and 5- or 1-substituted tetrazoles:



Thermal or photochemical decomposition of organic azides occurs with evolution of nitrogen to give the corresponding nitrenes. The latter contain monovalent nitrogen and, like carbenes, undergo isomerization, insertion reactions, or addition of nucleophiles. Many azide reactions, such as their frequently explosive decomposition, ring closure, Curtius or Schmidt reactions, photochemical cross-linking in polymer systems, and ring expansion, involve nitrene intermediates.

Hydrogenation Reactions. Azides can be reduced to the corresponding amines by hydrogen–palladium [98, 112], H_2S [113], triphenylphosphine (Staudinger reduction) [96], lithium aminoborohydrides [114], and other sources.

Azido- and Diazo Transfer. Imidazole-1-sulfonyl azide is the reagent of choice [72] for diazo transfer (Regitz diazo transfer [42]), whereas trisyl azide [41] has been used for azide transfer onto enolates.

9. Safety Precautions and Environmental Protection

In the production of sodium azide, sodium amide represents a dangerous material, because it reacts violently with water. Contact with water or air during storage must therefore be prevented. As the azide reaction continues, the

evolving hydrogen must be burned off outside the building or purified for further use.

All equipment and gas piping must be fitted with explosion valves or rupture membranes because all the evolved gases are explosive in a wide range of mixtures. The hazard is increased by airborne dust particles.

When handling sodium azide, its solutions, and highly volatile hydrazoic acid, impervious protective clothing must be worn. To protect the respiratory organs from dust or gases, dustproof masks must be used. Before the masks are put on, their blank metal parts must be lacquered, care being taken that the lacquer is free of pores. A supply of fresh air to the masks is advantageous.

Working materials should preferably be plastics, but nonsparking metals may also be used. Sodium azide moistened with water reacts violently when ignited, giving off a highly caustic smoke.

In the event of fire, water-containing extinguishers must not be used; dry sand and anhydrous soda (soda ash) are suitable.

Small amounts of azide-containing waste and azide dust can be decomposed harmlessly with ceric ammonium nitrate. Larger quantities must be destroyed by addition of a sodium nitrite solution followed by a mineral acid solution. Azides react with acids to give a gas cloud capable of spontaneous detonation.

Organic azides are considered safe when the sum of carbon and oxygen atoms divided by the number of nitrogen atoms exceeds three [7].

10. Economic Aspects

The main producers of azides are located in China, India, the United States, and Japan with a total annual production of 1 000 t for sodium azide [1]. Thereof the major part is used in the automobile safety devices.

11. Toxicology and Occupational Health

Dry sodium azide, its solutions, and hydrazoic acid are extremely toxic and can be absorbed by inhalation, ingestion, and skin absorption [37, 115]. In the event of contact of the skin

or mucous membranes with azides, the affected parts must be rinsed thoroughly with water. The MAK value for sodium azide is 0.2 mg/m³ and for hydrazoic acid, 0.1 mL/m³ \triangleq 0.18 mg/m³ [37]. Even minute amounts of azides cause headache, irritation of the eyes and mucous membranes, heightened irritability and excitation, impairment of vision, shortness of breath, reduction of blood pressure, risk of collapse, and fainting. The maximum nonfatal limit is given as 0.01 g; nevertheless, 0.005–0.01 g can have harmful effects.

Minor complaints can be eased quickly by fresh air or by administration of oxygen. No chronic poisoning has been observed.

Azides appear to be similar to cyanides and prussic acid, in their ability to affect the cytochrome oxidase system and probably become bound to methemoglobin; *p*-aminopropiophenone has been suggested as an antidote. Amyl nitrite, which is effective in prussic acid poisoning, increases the risk of collapse.

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